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10/584,443	08/17/2007	Jaume Pons	PC19492A	4751
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PFIZER INC 10555 SCIENCE CENTER DRIVE SAN DIEGO, CA 92121				
EXAMINER				
GUSLOW, ANNE				
ART UNIT		PAPER NUMBER		
1643				
NOTIFICATION DATE		DELIVERY MODE		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

-ipgslaj@pfizer.com

# Office Action Summary

**Application No.**

10/584,443

**Applicant(s)**

PONS, JAUME

**Examiner**

Anne M. Gussow

**Art Unit**

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 December 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 18-22 and 25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-16, 26 and 27 is/are rejected.
- 7) ☒ Claim(s) 17, 23 and 24 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/06)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☒ Other: Sequence alignments

### **DETAILED ACTION**

1. Claims 1-17, 23, 24, 26, and 27 have been amended.

Claims 18-22 and 25 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 3, 2009.

2. Claims 1-17, 23, 24, 26, and 27 are under examination.
3. The following office action contains NEW GROUNDS of Rejection.

### ***Objections Withdrawn***

4. The objection to the oath or declaration is withdrawn in view of applicant's supplemental application data sheet filed December 24, 2009.
5. The objection to the specification is withdrawn in view of applicant's amendment to the specification.

### ***Rejections Withdrawn***

6. The rejection of claims 1-17, 26, and 27 under 35 U.S.C. 101 as being directed to non-statutory subject matter is withdrawn in view of applicant's amendment to the claims.

***Rejections Maintained/ NEW GROUNDS of Rejection***

***Claim Objections***

7. Claims 23 and 24 remain objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from a multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits. In the instant case, claims 23 and 24 depend from claims 1 or 15 and claim 15 still depends from any of claims 1-5.
8. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim 4 depends from claim 1 which recites a heavy chain variable domain. It is presumed that applicant intended for claim 4 to depend from claim 2 which recites a light chain variable domain.

***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-4, 6-14, 26, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising three heavy chain CDR regions and three light chain CDR regions, does not reasonably provide enablement for an antibody comprising fewer than all 6 CDR regions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broadly drawn to an antibody comprising a single defined CDR. Although the claim language recites a CDR1, CDR2, and CDR3, applicant has defined only the heavy chain or only the light chain CDRs by SEQ ID No. When defining an antibody by CDR sequence it is necessary to define all six CDR sequences for the reasons set forth below. Further, some of the claims (for example, claims 1 and 3) read on an antibody comprising a heavy chain (or light chain) CDR, thus only a single CDR.

The specification discloses antibody constructs containing three heavy chain CDRs and three light chain CDRs. The specification does not disclose antibodies that bind to antigen and comprise fewer than all six CDR regions.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is

characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proceedings of the National Academy of Sciences, 1982. Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). De Pascalis, et al. (Journal of Immunology, 2002. Vol. 169, pages 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs

were used for the constructs (see page 3080, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by Casset, et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset, et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos, et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm, et al. (Molecular Immunology, 2007. Vol. 44, pages 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen, et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu, et al. (Journal of Molecular

Biology, 1999. Vol. 294, pages 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to produce a functional antibody comprising fewer than 6 CDR regions. The specification does not teach how to make an antibody that would bind trkC and comprise fewer than 6 CDR regions.

In view of the lack of the predictability of the art to which the invention pertains, undue experimentation would be required to make the claimed antibody with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce the claimed antibody and absent working examples providing evidence which is reasonably predictive that the claimed antibodies are effective binding molecules, commensurate in scope with the claimed invention.

### ***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the

applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-16, 26, and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Shelton (WO/2004/058190, priority to December 23, 2002).

The claims recite an isolated agonist anti-trkC antibody comprising a heavy chain CDRs comprising: (a) a CDR1 of the formula GYTFTSYXaaXaaH (SEQ ID NO:16), wherein Xaa at position 8 is R or W, and Xaa at position 9 is I, L, R, or M; (b) a CDR2 of the formula EIYPSNXaaRTNYNEKFxaaS (SEQ ID NO:17), wherein Xaa at position 7 is A, T, S, or G; and Xaa at position 16 is K or E; and (c) a CDR3 of the formula KYYGNGXaaXaaRSWYFDV (SEQ ID NO:18), wherein Xaa at position 7 is T or S; wherein Xaa at position 8 is R, Q, K, S, or Y; wherein the agonist anti-trkC antibody is not an antibody comprising a heavy chain CDRs comprising a CDR1 region of SEQ ID NO:22, a CDR2 region of SEQ ID NO:23, and a CDR3 region of SEQ ID NO:24, wherein the agonist anti-trkC antibody further comprises a light chain variable region.

An isolated agonist anti-trkC antibody comprising a light chain CDRs comprising: (a) a CDR1 of the formula RASESXaaDXaaYGISFXaaXaa (SEQ ID NO:19), wherein Xaa at position 6 is I or V; Xaa at position 8 is N or S; Xaa at position 14 is L or M; Xaa at position 15 is A, T, or N; (b) a CDR2 of the formula AASNxXaaGS (SEQ ID NO:20), wherein Xaa at position 5 is R, L, or Q; and (c) a CDR3 of the formula QQSKXaaVPRT (SEQ ID NO:21), wherein Xaa at position 5 is T, A, S, or E; wherein the agonist anti-trkC antibody is not an antibody comprising a light chain CDRs comprising a CDR1 region of SEQ ID NO:25, a CDR2 region of SEQ ID NO:26, and a CDR3 region of SEQ

ID NO:27. An isolated agonist anti-trkC antibody comprising: (a) a heavy chain CDRs comprising: (i) a CDR1 of the formula GYTFTSYXaaXaaH (SEQ ID NO:16), wherein Xaa at position 8 is R or W, and Xaa at position 9 is I, L, R, or M; (ii) a CDR2 of the formula EIYPSNXaaRTNYNEKFxaaS (SEQ ID NO:17), wherein Xaa at position 7 is A, T, S, or G; and Xaa at position 16 is K or E; and (iii) a CDR3 of the formula KYYYGNXaaXaaRSWYFDV (SEQ ID NO:18), wherein Xaa at position 7 is T or S; wherein Xaa at position 8 is R, Q, K, S, or Y; and (b) a light chain CDRs comprising: (i) a CDR1 of the formula RASESXaaDXaaYGISFXaaXaa (SEQ ID NO:19), wherein Xaa at position 6 is I or V; Xaa at position 8 is N or S; Xaa at position 14 is L or M; Xaa at position 15 is A, T, or N; (ii) a CDR2 of the formula AASNxaaS (SEQ ID NO:20), wherein Xaa at position 5 is R, L, or Q; and (iii) a CDR 3 of the formula QQSKXaaVPRT (SEQ ID NO:21), wherein Xaa at position 5 is T, A, S, or E; wherein the agonist anti-trkC antibody is not an antibody comprising (a) a heavy chain CDRs comprising a CDR1 region of SEQ ID NO:22, a CDR2 region of SEQ ID NO:23, and a CDR3 region of SEQ ID NO:24; and (b) a light chain CDRs comprising a CDR1 region of SEQ ID NO:25, a CDR2 region of SEQ ID NO:26, and a CDR3 region of SEQ ID NO:27, wherein the agonist anti-trkC antibody binds human trkC, wherein the agonist anti-trkC antibody binds to human trkC with a KD less than about 5 nM, wherein the agonist anti-trkC antibody further binds rodent trkC, wherein the agonist anti-trkC antibody is a monoclonal antibody, wherein the agonist anti-trkC antibody is a humanized antibody, wherein the agonist anti-trkC antibody comprises a heavy chain variable region comprising: (a) a CDR1 region of SEQ ID NO:4; (b) a CDR2 region of SEQ ID NO:5;

and (c) a CDR3 region of SEQ ID NO:6, wherein the heavy chain variable region consists of the sequence of SEQ ID NO:1, wherein the agonist anti-trkC antibody comprises a light chain variable region comprising: (a) a CDR1 region of SEQ ID NO:7; (b) a CDR2 region of SEQ ID NO:8; and (c) a CDR3 region of SEQ ID NO:9, wherein the light chain variable region consists of the sequence of SEQ ID NO:2. An isolated agonist anti-trkC antibody of any of claims 1-5, wherein the agonist anti-trkC antibody comprises (a) a heavy chain variable region comprising: (i) a CDR1 region of SEQ ID NO:4; (ii) a CDR2 region of SEQ ID NO:5; and (iii) a CDR3 region of SEQ ID NO:6; and (b) a light chain variable region comprising: (i) a CDR1 region of SEQ ID NO:7; (b) a CDR2 region of SEQ ID NO:8; and (c) a CDR3 region of SEQ ID NO:9, wherein the heavy chain variable region consists of SEQ ID NO:1, and the light chain variable region consists of the sequence of SEQ ID NO:2.

Shelton teaches antibodies that bind to trkC comprising the CDR regions of SEQ ID Nos. 4, 5, 6, 7, 8, and 9 (see sequence alignments). The sequences of the instant SEQ ID Nos. 16, 17, 18, 19, 20, and 21 comprise the sequences of SEQ ID Nos. 4-9 respectively because of the variable positions in SEQ ID Nos. 16-21. Shelton teaches the trkC antibodies comprise the heavy chain variable region of SEQ ID No. 1 and the light chain variable region of SEQ ID No. 2 (see sequence alignments and tables 1 and 2). Shelton teaches the anti-trkC antibodies may bind both human and rodent trkC and may be a monoclonal antibody or a humanized antibody (paragraph 15). Shelton teaches the binding affinity of the A5 antibody (comprising SEQ ID Nos. 1 and 2) is 0.28nM (paragraph 88). Since Shelton teaches an antibody that binds to trkC

comprising sequences that are identical to the instant SEQ ID Nos. 1, 2, and 4-9, all the limitations of the claims have been met.

13. Claims 1-16, 26, and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Shelton (US PG PUB 2007/0014786, priority to March 20, 2003).

The claims have been described supra.

Shelton teaches antibodies that bind to trkC comprising the CDR regions of SEQ ID Nos. 4, 5, 6, 7, 8, and 9 (see sequence alignments). The sequences of the instant SEQ ID Nos. 16, 17, 18, 19, 20, and 21 comprise the sequences of SEQ ID Nos. 4-9 because of the variable positions. Shelton teaches the trkC antibodies comprise the heavy chain variable region of SEQ ID No. 1 and the light chain variable region of SEQ ID No. 2 (see sequence alignments and tables 1 and 2). Shelton teaches the anti-trkC antibodies may bind both human and rodent trkC and may be a monoclonal antibody or a humanized antibody (paragraph 14). Shelton teaches the binding affinity of the A5 antibody (comprising SEQ ID Nos. 1 and 2) is 0.28nM (paragraph 72). Since Shelton teaches an antibody that binds to trkC comprising sequences that are identical to the instant SEQ ID Nos. 1, 2, and 4-9, all the limitations of the claims have been met.

### ***Conclusion***

14. Claims 1-16, 26, and 27 are rejected.

Claims 23 and 24 are objected to.

Claim 17 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow  
March 18, 2010

/Anne M. Gussow/  
Examiner, Art Unit 1643